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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,282	04/14/2004	Donald Bellgrau	3921-1-1-1-1	7928

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/825,282	BELLGRAU ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43,45-50,54,55 and 64-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43,45-50,54,55 and 64-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date __.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 10/18/07 has been acknowledged.

Claims 1-43, 45-50, 54-55, 64-70 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **571-273-8300.**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 102

In response to applicants declaration(s) that the invention as claimed was conceived to actual reduction to practice prior to at least Dec. 10, 1998 (Exhibit A), the prior art rejections under 35 USC 102(a) and (f) as being anticipated by Shinoura et al, Human Gene Therapy 9(18):2683-2689, 1998 and Hedlund et al Cell Death and Differentiation 6:155-182, 1999 are withdrawn.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting

directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-43, 65, 67 and 70 are rejected under 35 U.S.C. 102(e) as being anticipated by Bruder et al (US 6,391,612, 2002).

Bruder et al teaches a method of in vitro propagation of a viral e vector comprising a deleterious gene (cytostatic, cytotoxic, or apoptotic, gene) in isolated host cells, wherein the host cells comprises a blocking gene (anti-apoptotic) that inhibits the adverse effects of the deleterious gene on the host- cells (see abstract, col.2 lines 15-32). The cited art further teaches that the blocking gene can be any suitable gene and can be derived from a viral or cellular source which is capable of blocking the deleterious effects on the host-production cell. The cited art teaches that the examples of blocking genes include, but are not limited to, genes that encode **crmA**, a caspase inhibitor such as baculoviral p35 or an IAP gene product, a FLIP gene product, and adenoviral 14.7 K protein (see col.4 lines 9-14). The cited art further teaches that the deleterious gene can be any suitable gene of interest, including genes that encode **FasL**, FADD, or FLICE, other caspases, I.kappa.B, adenoviral E4/ORF4, adenoviral E1A products, TNF receptor, TRAIL receptor, Bcl-Xs, DR5 and RAID (see col.4, lines 27-31). The cited art further teaches that the deleterious effects of any particular gene product can vary from host-production cell to host-production cell and accordingly, the deleterious effect of a deleterious gene product is defined by the action of the gene product on a cell commonly used to propagate viral vectors (col.4, lines 37-46 also see col.5, lines 33-45). The cited art further teaches that the passage of the **AdFasL/G** stock on HEK-293 cells comprising the blocking gene crmA yielded significantly higher levels of virus, averaging in the range of about 600 to about 1200 pfu/cell. The cited art teaches that the expression of a blocking gene, such as crmA, in host production cells, such as HEK-293 cells, enables the improved production of a viral eukaryotic gene transfer vector comprising a deleterious gene, such as the AdFasL/G vector, which comprises a deleterious gene that induces apoptosis (see col.8, Example-1). The cited

art further teaches that the co-transfection of HEK-293 cells with the CrmA or 14.7 K expression plasmids reduces the level of apoptosis to less than about 30% and, in some instances, to less than about 20%. The cited art demonstrates that the expression of crmA and adenoviral 14.7 K can advantageously reduce the level of apoptosis in the host-production cell (e.g., HEK-293 cells or A549 cells), which can in turn allow for higher yields of viral eukaryotic gene transfer vectors comprising a deleterious gene (see col.10, example-5, also see col. 11-12). Furthermore, the nucleic acid of encoding Fas-ligand and CrmA are inherently disclosed by the cited prior art, since the art teaches the nucleic acid construct containing CrmA and Fas-ligand gene sequences. Thus the cited art clearly anticipated the invention as claimed.

Claim Rejections - 35 USC § 112

Claims 45-50, 54-55, 64, 66, and 68-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reason of record as set forth in the office action mailed on 04/18/07.

The instant invention relates to a method for cancer gene therapy by inducing apoptosis. The scope of invention as claimed encompasses a method of inducing apoptosis in any cancer cell of a recipient mammal by administering a recombinant viral vector comprising CrmA and Fas ligand, wherein the expression of Fas Ligand is sufficient to produce elimination of tumor cells, inhibition of tumor growth and inhibition of metastasis (see claim 54). The scope of invention as claimed further encompasses inducing apoptosis in any cancer cell by introducing a viral vector encoding Fas Ligand (see claim 64).

The applicant argues that encoding Fas Ligand in any tumor cell in-vitro or in-vivo would induce apoptosis. The applicant argues that example-13 of the specification

enables the invention as claimed *(i.e. transplantion of ex-vivo AdFasL-transfected prostrate tumor cells fails to produce tumors in transplanted mice)*. The applicant included several post filing publications to support the specification and provide further demonstrations *(via post filing art)* that administration of a nucleic acid molecule, and particularly a viral vector, encoding Fas ligand, or a cell that has been transduced with such a nucleic acid molecule, is effective in-vivo to reduce tumor burden.

However, the applicant's arguments are found not persuasive. Applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The MPEP 2164.05(a) clearly states that the specification must be enabling as of the filing date *(i.e. 05/17/1999 in instant case)*. Applicant is reminded that developments occurring after the fling date of an application are of no significance regarding what one skilled in the art believed as of that filing date. See for example, in re Wright, 27 USPQZd 1510, 1514 (Fed. Cir. 993). Furthermore the state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b). The court has already held that post-filing disclosures can not be used to support the enablement of earlier filed specifications. *In re Glass*, 181 USPQ 31, 34 (CCPA 1974).

As stated above and earlier the specification (as filed) fails to teach induction of apoptosis in any and all kinds of tumors *(solid or systemic and with metastatic potential)* even via direct injection, which would result in the reduction or elimination of tumor in-vivo. For example the specification as filed fails to disclose the treatment of leukemia via method for gene therapy by administering Adenoviral vector comprising gene encoding CrmA and Fas- Ligand. The earlier office action provides clear evidence that cancer gene therapy is considered highly unpredictable and suppression of tumor growth via ex-vivo transfection tumor cells lines followed by implantation in mice does not recapitulate the complexities involved in the cancer treatment and especially cancer gene therapy. For example it is unclear how one skill in the art would target cancer cells

circulating in the systemic circulation in view of applicant's disclosure and scope of invention as claimed. (i.e. using any portion of SEQ ID NO:4). Furthermore, in-vitro gene transfer studies are not predictive of in-vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in-vivo environment.

In instant case treatment of any cancer using any viral vector that encodes Fas-Ligand and CrmA via a method of gene therapy is not considered routine in the art and without an enabling disclosure the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SUMESH KAUSHAL
PRIMARY EXAMINER